

**Amendments to the Drawings**

The attached sheet of drawing includes changes to Figure 5. This sheet, which includes Figure 5, replaces the original sheet including Figure 5. In Figure 5, previously omitted element 511 has been added, and a typographical error has been corrected in Figure 5 a) so that the label of element 503/515 correctly identifies the element.

Attachment: Replacement Sheet  
Annotated Sheet Showing Changes

**REMARKS**

Claims 197, 199 to 200 and 202 to 214 are pending in this application. Claims 197, 202, 203, 204, 206, 207, 208, 213 and 214 have been amended. No new matter has been added by these claim amendments.

The amendments to claims 197 and 202 are supported throughout the specification as filed. Support for the term “an essentially flat surface” can be found, for example, at page 14, line 24 – page 15, line 1 and Figures 1 and 2. Support for the term “a plurality of magnet s are contained in said substrate” can be found, for example, at page 9, lines 4 – 8 and Figures 1 and 2. Support for the term “said plurality of magnets are arrayed in said substrate such that each magnet defines a localized magnetic field gradient to define a magnetic area” can be found, for example, at page 9, lines 4 – 8 and page 16, lines 4 – 7. Support for the term “said magnetic area is situated on the surface of the substrate in a predetermined location discrete from other magnetic areas, wherein the plurality of magnetic areas defined by said plurality of magnets are disposed in a two-dimensional array on the substrate” can be found, for example, at page 15, lines 19 – 20; page 24, lines 14 – 22; page 5, lines 11 – 15, and Figures 1 and 2.

The amendments to claim 203 are supported throughout the specification as filed. Support for the term “a membrane containing a plurality of wells that match the plurality of the magnetic areas” may be found, for example, at page 36, lines 7 – 9. Support for the term “said cell isolation device is placed on said substrate” may be found, for example, at page 32, lines 1 – 5, which refer to Figure 5.

Support for the amendment to claim 204 can be found, for example, at page 32, lines 20 – 22, which refer to Figure 5 a).

Support for the amendment to claim 204 can be found, for example, at page 33, lines 1 – 7, which refer to Figure 5 a).

The amendments to claims 207 and 208 are supported throughout the specification as filed. Support for the term “said plurality of magnetic areas further comprises immobilized cells associated with said magnetic material” may be found, for example, at page 5, lines 11 – 15 and at page 31, lines 20 – 22. Support for the term “the cell isolation device is placed on said substrate” may be found, for example, at page 32, lines 1 – 5; at page 32, lines 20 – 22; and at

page 33, lines 20-22, all of which refer to Figure 5. Support for the term “said cells are capable of being transferred from said plurality of magnetic receptacles to said cell isolation device” may be found, for example, at page 31, line 23 – page 32, line 1 and at page 34, lines 1 – 11.

Support for the amendment to claim 213 can be found, for example, at page 17, line 25 – page 18, line 10.

Support for the amendment to claim 214 can be found, for example, at page 19, line 24 – page 20, line 5.

### **OBJECTION TO THE SPECIFICATION**

The disclosure is objected to because Figure 5 does not contain “511” as a label designating magnetic receptacles. Applicants submit herewith a corrected sheet containing Figure 5 where magnetic receptacles “511” has been added to the figure. Support for the amendment can be found, for example, at page 31, lines 22 – 23 (describing the relative position of the magnetic receptacles to the substrate) and in Figures 1 b) and 2 b) (depicting the relative position of the magnetic receptacles to the substrate). As such, Applicants respectfully request the withdrawal of the objection.

Additionally, a typographical error has been corrected in Figure 5 a) so that the label of element 503/515 correctly reads so. Support for the amendment can be found, for example, in Figure 5 b).

### **REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH – WRITTEN DESCRIPTION**

Claims 197, 199, 200, and 202-214 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejections. However, to advance prosecution, Applicants have amended independent claim 197 to recite “said magnetic area is situated on the surface of the said substrate.” Support can be found, for example, at page 15, lines 19 – 20 of the specification and in Figures 1b) and 2b). As such, Applicants respectfully request the withdrawal of the rejections.

## REJECTIONS UNDER 35 U.S.C. § 112, SECOND

### PARAGRAPH - DEFINITENESS

Claims 197, 199, 200, and 202-214 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse the rejections.

a) Specifically, the Examiner contends that the scope of the term “associated with” is uncertain. With regard to the first “associated with” in line 6 of claim 197, Applicants have amended the claim to delete the term, thus rendering the rejection moot. With regard to the second “associated with” in line 8 of claim 197, Applicants submit that the term refers to the association between the cells and the magnetic material. Such association is defined clearly at page 9, line 16 through page 10, line 7 as “related to either adhering magnetic material to a cell surface, penetrating magnetic material through the plasma membrane or by having cells phagocytose or pinocytose magnetic material.”

b) The Examiner contends that the structure of the magnetic receptacles has not been set forth in a manner that will allow cells to be immobilized within the magnetic receptacles. Applicants have amended the claims in accordance with the Examiner Interview to clarify the structure of the magnetic receptacles (i.e. areas). Independent claim 197, as amended, now recites “said device comprising a substrate having an essentially flat surface, wherein a plurality of magnets are contained in said substrate, wherein said plurality of magnets are arrayed in said substrate such that each magnet defines a localized magnetic field gradient to define a magnetic area, wherein said magnetic area is situated on the surface of the substrate in a predetermined location discrete from other magnetic areas, wherein the plurality of magnetic areas defined by said plurality of magnets are disposed in a two-dimensional array on the substrate, wherein said localized magnetic field gradient can immobilize one to about five cells within said each of said plurality of magnetic areas.”

c) The Examiner contends that claim 203 and its dependent claims are confusing and unclear as to structure that is a cell isolation device and how the device is mated with the substrate to isolate cells. In accordance with the Examiner Interview, Applicants have amended claim 203 to clarify the structure of the cell isolation device. Applicants submit that, as stated in line 18, page 31 – line 9, page 32 and as illustrated in Figure 5, the cell isolation device

comprises a membrane that contain wells. When the membrane is placed on the substrate, the periodicity of the wells match that of the magnetic areas on the substrate. The membrane inhibits fluid communication between the immobilized cells in each magnetic area. Additionally, lines 10-19 on page 32 disclose examples of the material and methods to make such membrane. As such, one of ordinary skill in the art would understand the structure of the cell isolation device and how it is placed on the substrate.

d) The Examiner contends that the term “matching periodicity” in claim 203 is uncertain as to meaning and scope. In accordance with the Examiner Interview, Applicants have amended the claims to clarify that the wells match the magnetic areas when the cell isolation device is placed on the substrate. Applicants point out that the term “periodicity” with regard to magnetic receptacles (i.e. areas) has been defined at page 17, lines 12-14 as “the distance between respective vertical centerlines between adjacent magnetic receptacles or adjacent magnetic receptacles on/in the substrate of the device.” As such, one of ordinary skill in the art would know when periodicity exists, and whether such periodicity is matching or not matching.

e) The Examiner contends that claim 204 is confusing because the device has not been previously required to have wells, and it is uncertain how the wells function for cell isolation in relation to the magnetic receptacles. Applicants submit that independent claim 203 has been amended to set the antecedent basis for wells and to clarify the structure of the cell isolation device. Because the cell isolation device has a membrane that inhibits fluid communication between the immobilized cells in each magnetic area, these cells are capable of being isolated into wells.

f) The Examiner contends that claim 207 is unclear as to the structure of the cell separation device that allows separation of the device from the substrate while cells remain in the cell isolation device. In accordance with the Examiner Interview, Applicants have amended claim 207 to clarify the structure. Applicants submit that because the periodicity of the wells matches that of the magnetic areas, cells immobilized within each magnetic area are also physically located within the corresponding well of the cell isolation device. Once the substrate (hence the magnetic field and magnetic force that immobilizes the cells on the substrate) is removed, the cells are capable of being transferred from the substrate to the cell isolation device and remaining in the cell isolation device.

g) The Examiner contends that claim 208 is unclear as to the structure of the cell isolation device that enables it to be mated to the receptacles and function in relation to centrifugal force as claimed. In accordance with the Examiner Interview, Applicants have amended claim 207, from which claim 208 depends, to clarify the structure that enables the cell isolation device and the magnetic areas to function together in relation to centrifugal force. Applicants further submit that lines 1-11 on page 34 clearly set down example of how such cell isolation device functions by use of centrifugal force. In this example, the cell isolation device is placed on the substrate, and a centrifugal force is applied. Cells immobilized on the substrate are spun into the wells of the cell isolation device. The cell isolation device and the substrate are then inverted, and the substrate removed.

h) The Examiner contends that claim 214 is unclear as to material that is a highly permeable magnetic material. In accordance with the Examiner Interview, Applicants have amended claim 214 to recite “highly-magnetically-permeable material.” Applicants further submit that the term “highly-magnetically-permeable material” has been clearly defined in lines 11-14 on page 20. A “highly-magnetically-permeable material” is characterized by having a high relative magnetic permeability ( $\mu_r$ ) which is the permeability of the material ( $\mu$ ) relative to the magnetic permeability of free space ( $\mu_0$ ) as generally defined by the equation  $\mu_r = \mu/\mu_0$ .” Examples of highly-magnetically-permeable material are also given. As such, one of ordinary skill in the art would understand what a highly permeable magnetic material is.

For at least the reasons stated above, Applicants respectfully request the withdrawal of the rejections.

#### **REJECTIONS UNDER 35 U.S.C. § 103 - OBVIOUSNESS**

Claims 197, 199, 200, and 202-214 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ekenberg *et al.* (5,567,326) in view of Dolan *et al.* (6,136,182) and Liberti *et al.* (6,013,532), and, if necessary, in further view of Zborowski *et al.* (5,968,820). Applicants respectfully traverse the rejections.

The Examiner asserts that: (1) Ekenberg discloses “an apparatus for separating magnetically responsive particles” containing “magnetically responsive pins in a pin plate that form a pin array;” (2) Dolan discloses a device for collecting “magnetically labeled cells . . . on

an interior surface of a vessel in an ordered array,” and (3) Liberti discloses “magnetic immobilization and manipulation of cells.”

The Examiner contends that it would have been “obvious to modify the apparatus of Ekenberg *et al.* by **replacing the pins with . . . magnets . . . so that cells are drawn to and immobilized on the bottom surface of each well** as suggested by Dolan *et al.* . . . and[, as per] Liberti *et al.* [,] placing a vessel into a magnetic field . . . where magnetically-labeled cells are attracted toward the collection surface and immobilized thereon in a linear array.”

Applicants respectfully point out that the Examiner has failed to establish a *prima facie* case of obviousness. As discussed during the Examiner Interview, Ekenberg *et al.* expressly teach away from the modification as suggested by the Examiner. The device as instantly claimed has magnets in the substrate and outside the receptacles or wells in which cells are located. Ekenberg *et al.* discloses a device with magnetic pins located inside the reaction tubes. In Column 2, lines 26 – 35, Ekenberg *et al.* distinguish from other magnetic separators with magnets outside the reaction tubes by stating that such magnetic separators “have the disadvantage that the magnetic capture is accomplished by using positionally-fixed magnets placed external to the wall of the tube of the reaction vessel, and the magnetic particles are collected on the side of the tube. To release the particles, the vessel must be removed from the field of the magnets. This technique is very cumbersome when attempting to separate and process a large number of samples ....” As such, one of ordinary skill in the art would not modify Ekenberg *et al.* to replace the internal magnetic pins with external magnets, as suggested by the Examiner.

The deficiency of Ekenberg *et al.* is not cured by Dolan *et al.*, Liberti *et al.*, or Zborowski *et al.*. In Dolan *et al.*, Liberti *et al.*, and Zborowski *et al.*, the magnets are located outside the vessel or flow assembly in order for the cells to be collected/sorted. For example, Dolan *et al.* disclose an “external magnetic gradient which moves magnetically responsive particles to a region of a collection vessel.” *See* col. 6, lines 42 – 44. Liberti *et al.* disclose vessels that are placed “between” the magnets. *See* col. 6, lines 60 – 63; Figure 1A; col. 11, lines 35 – 39; Figures 4A and 4B. Zborowski *et al.* disclose a flow channel “in between” the magnets. *See* col. 12, lines 2 – 6 and Figure 3. Therefore, none of Dolan *et al.*, Liberti *et al.*, or Zborowski *et al.*

provides motivation to combine the device of Ekenberg *et al.*, which teaches away from using external magnets, with the cell collecting/sorting mechanisms disclosed in the references.

For at least the reasons stated above, a *prima facie* case of obviousness has not been established. Applicants respectfully request the withdrawal of the rejections.

## CONCLUSION

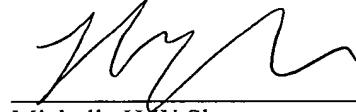
Applicants submit that the foregoing amendments respond to the Office Action of June 29, 2006 and that the claims are in condition for allowance. Applicants authorize the Commissioner to charge any fee due or credit any overpayment arising from this communication to Kenyon & Kenyon LLP **Deposit Account No. 11-0600**.

The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

KENYON & KENYON LLP



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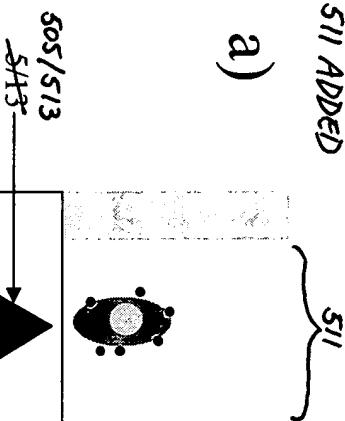
Dated: October 30, 2006

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Figure 5

ELEMENT 5II ADDED

a)



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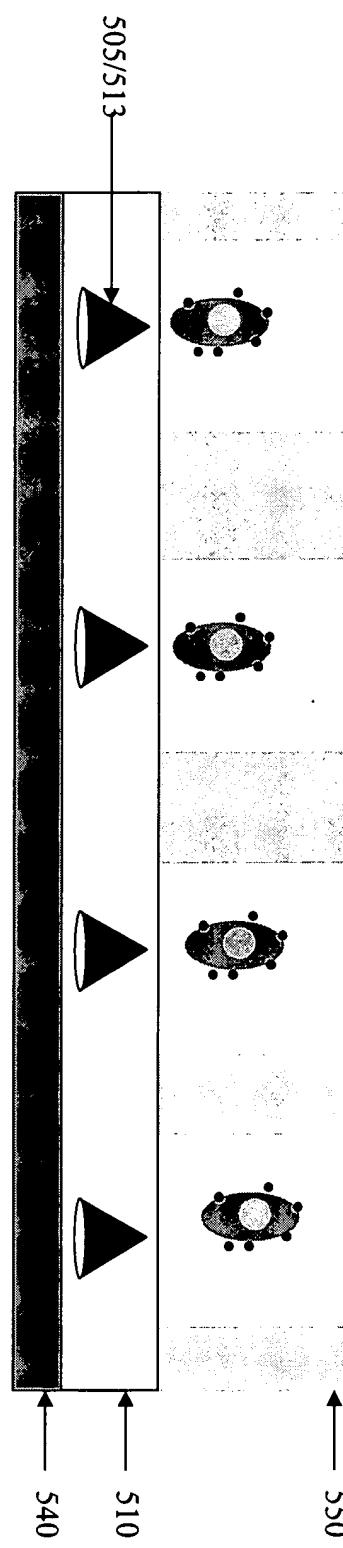
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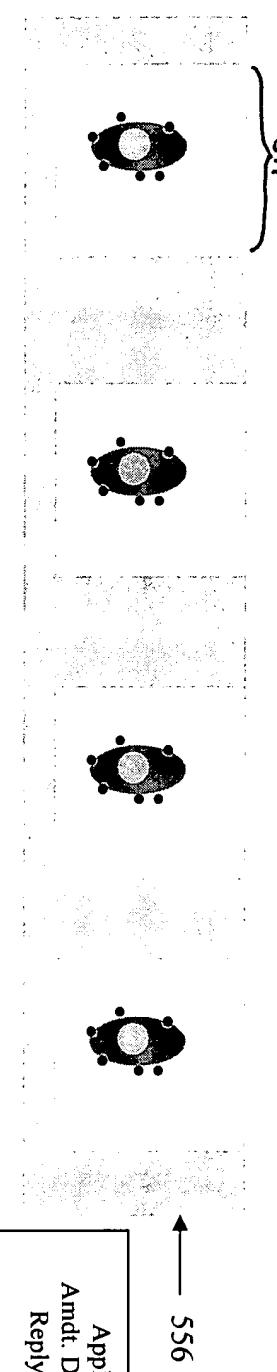
ELEMENT 5II ADDED

b)



ELEMENT 5II ADDED

c)



ELEMENT 5II ADDED

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June 29, 2006

Annotated Sheet Showing Changes

